

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US2004/041970

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D405/14 C07D409/14 C07D401/14 C07D417/14 A61K31/506
A61P37/00 A61P11/06 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 283 056 A (ESAI CO., LTD.) 12 February 2003 (2003-02-12) the whole document	1-34
X	WO 03/035639 A (EISAI CO., LTD.) 1 May 2003 (2003-05-01) the whole document	1-34
P, X, L	~& EP 1 439 175 A 21 July 2004 (2004-07-21) counterpart in English	1-34
X	WO 01/62233 A (F. HOFFMANN LA ROCHE AG) 30 August 2001 (2001-08-30) the whole document	1-34
A	WO 02/47690 A (CYTOVIA, INC.) 20 June 2002 (2002-06-20) * the whole document, particularly examples 109-114 *	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

4 April 2005

Date of mailing of the international search report

20/04/2005

Name and mailing address of the ISA

European Patent Office, P.B. 6816 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 661 epo nl,
Fax (+31-70) 340-3010

Authorized officer

Allard, M

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 690068.601PC	FOR FURTHER ACTION	See item 4 below
International application No. PCT/US2004/041970	International filing date (<i>day/month/year</i>) 14 December 2004 (14.12.2004)	Priority date (<i>day/month/year</i>) 15 December 2003 (15.12.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant ALMIRALL PRODESFARMA AG		

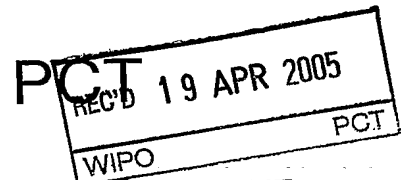
1.		This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 <i>bis</i> .1(a).																								
2.		<p>This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.</p>																								
3.		<p>This report contains indications relating to the following items:</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 10%; text-align: center;"><input checked="" type="checkbox"/></td> <td style="width: 30%;">Box No. I</td> <td style="width: 60%;">Basis of the report</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<input type="checkbox"/>	Box No. II	Priority	<input checked="" type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input type="checkbox"/>	Box No. VI	Certain documents cited	<input type="checkbox"/>	Box No. VII	Certain defects in the international application	<input type="checkbox"/>	Box No. VIII	Certain observations on the international application
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<input type="checkbox"/>	Box No. VIII	Certain observations on the international application																								
4.		The International Bureau will communicate this report to designated Offices in accordance with Rules 44 <i>bis</i> .3(c) and 93 <i>bis</i> .1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44 <i>bis</i> .2).																								

<p style="text-align: center;">The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No. +41 22 740 14 35</p>	<p>Date of issuance of this report 20 June 2006 (20.06.2006)</p> <p>Authorized officer Ellen Moyse</p> <p>Telephone No. +41 22 338 89 75</p>
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PATENT COOPERATION TREATY

AdS

From the
INTERNATIONAL SEARCHING AUTHORITY



To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/041970

International filing date (day/month/year)
14.12.2004

Priority date (day/month/year)
15.12.2003

International Patent Classification (IPC) or both national classification and IPC
C07D405/14, C07D409/14, C07D401/14, C07D417/14, A61K31/506, A61P37/00, A61P11/06, A61P9/00

Applicant
ALMIRALL PRODESFARMA, SA.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Allard, M

Telephone No. +31 70 340-2002



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/041970

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/041970

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 24-28 (as to industrial applicability only)

because:

- ☒ the said international application, or the said claims Nos. 24-28 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/041970

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-34
	No: Claims	-
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-34
Industrial applicability (IA)	Yes: Claims	1-23, 29-34
	No: Claims	-

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 24-28 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: EP-A-1 283 056 (EISAI CO., LTD.) 12 February 2003 (2003-02-12)
- D2: WO 03/035639 A (EISAI CO., LTD.) 1 May 2003 (2003-05-01)
- D3: WO 01/62233 A (F. HOFFMANN LA ROCHE AG) 30 August 2001 (2001-08-30)

Note that for convenience the counterpart in English EP 1 439 175 of D2 is used in this opinion.

Novelty (Article 33(2) PCT)

The compounds of formula (I) according to claim 1 are not disclosed in the available prior art: the subject-matter of claims 1-34 is therefore novel.

Inventive step (Article 33(3) PCT)

D1, which is considered to represent the closest prior art, describes pyrimidine derivatives useful as adenosine A_{2b} receptor antagonists, see claims 14 and 17. In particular, D1 specifically discloses pyrimidin-2-amines substituted in positions 4 and 5 by heteroaryl groups as such derivative, see examples 3, 6, 7, 39, 42-46, 48 and 50.

Similar compounds with the same biological activity are disclosed in D2 and D3.

In the light of the teachings of D1, the problem underlying and solved by the present application can be seen in the provision of further compounds with the same biological activity.

To solve this problem, the present application proposes to interchange the substituents in positions 2 and 4 of the pyrimidine compounds disclosed in D1, *i.e.* to replace the 2-amino-4-heteroaryl substructure of the compounds of D1 by a 4-amino-2-heteroaryl substructure.

Such a modification would however appear to be an obvious measure in the design of further biologically active compounds, which does not involve an inventive step. It is in particular noted that D1 already suggests 4-aminopyrimidines as adenosine A_{2b} receptor antagonists (see in claim 14 the definition of R²), whereas D3 suggests a 2,4,6-substitution pattern on the pyrimidine core for similar adenosine A_{2b} receptor antagonists (see in particular D3, example 388).

The subject-matter of claims 1-34 does therefore not involve an inventive step.

Industrial applicability (Article 33(4) PCT)

The compounds, compositions and processes of claims 1-23 and 29-34 can be used in the pharmaceutical industry.

For the assessment of the present claims 24-28 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims.